Chapter 54
Should there be hormone replacement therapy for aging men?

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In contrast to the abrupt decline in hormone concentrations experienced by females during menopause, male hormone levels, on average, decline gradually and progressively as men age. However it is important to note that aging alone does not cause a significant decline in serum testosterone levels over time. The decline in testosterone over time is due mainly to the development of co-morbid conditions, such as diabetes, obesity, and metabolic syndrome. On average, several anabolic hormones, including testosterone, dehydroepiandrosterone (DHEA) and growth hormone (GH), experience physiologic decreases in serum concentration in older men when compared to younger men. In young adults, deficiencies in these hormones can lead to symptoms such as lethargy, decreased libido, changes in mood, and erectile dysfunction. Additionally, when younger men with documented hormone deficiencies are treated with hormone replacement therapy, there is frequent resolution of these symptoms as hormone levels normalize. Therefore, this raises the question of whether hormone replacement therapy in older men may alleviate or resolve some of the changes seen in body composition, mood, cognition, sexual function, and bone density as men age. Unfortunately, there is still limited knowledge regarding the complete benefits of hormone replacement in older men and the observed effects of therapy are frequently modest. Many of the symptoms of aging may be related to other co-morbidities or drug effects that are unrelated to the observed changes in serum hormone concentrations. In addition, there are potential adverse effects observed often with hormone replacement therapy which must be considered as well.

Testosterone

Beginning at approximately 40 years of age, testosterone levels in men begin to decline at annual rates of 1.0% for total testosterone

and 1.2% for free testosterone. This results in the mean plasma testosterone level of men in their seventh decade being 35% lower than that of younger men. There is also a corresponding observed increase in the concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone binding globulin (SHBG), with the increased SHBG concentration accounting for the greater rate of decline of free testosterone compared to total testosterone. However, although there is an overall average decrease in serum testosterone levels as men age, it is important to recognize that these levels may never fall below the lower limit of normal for many men. The prevalence of low testosterone in elderly men is typically cited to be between 10% - 25%.

The most common presenting symptoms of testosterone deficiency include sexual dysfunction, primarily decreased libido and erectile dysfunction, alongside changes in energy level and mood. While bothersome for patients, these symptoms are not themselves life threatening. However, it is prudent to identify testosterone deficiency in older men and not dismiss complaints as common symptoms of aging, given the correlations observed between prolonged testosterone deficiency and several more life-threatening issues. Testosterone deficiency has been positively associated across numerous studies with the development of adverse metabolic outcomes, including obesity, metabolic syndrome, and type 2 diabetes, as well as coronary artery disease, osteoporosis and decreased cognitive abilities (Chapter 64).

Testosterone deficiency is associated with decreased bone mineral density in men of any age. Several studies have documented the ability of testosterone replacement therapy (TRT) to improve bone mineral density in younger men (<50 years). However, recent randomized control trials and subsequent meta-analysis showed that TRT in men above the age of 60 years with low testosterone did not significantly reverse the tendency towards decreasing bone mineral density. While there is currently no evidence to support that TRT decreases the incidence of fracture among older men, there are numerous studies demonstrating that bone mineral density increases in men on TRT.

Testosterone is also believed to influence body composition and functional status. Over the past decade, many randomized control trials and meta-analyses have investigated the effects of TRT on muscle mass and physical functioning in elderly men over a short period (< 2 years). There was some disagreement amongst the studies, but most reported that TRT produced no significant change in

muscle strength with only a modest positive effect on physical function. Studies in which TRT was administered over a longer period (≥ 3 years) do report statistically significant increases in muscle mass and strength with TRT compared to placebo; however, the overall changes were modest. When compared against resistance weight training in elderly men, TRT has not shown to be superior although it may augment the progress made when TRT is combined with resistance training.

The complete role of testosterone on cognitive function in aging men has yet to be fully understood, but it has long been hypothesized that low testosterone levels may precipitate declines in or worsen cognitive functioning in the elderly. In a recent multi-center randomized clinical trial studying the effect of TRT in hypogonadal elderly men with established age associated memory impairment, there was no improvement in memory or other tests of cognitive function over a one-year period when compared to baseline testing or placebo. The results of this trial are consistent with other smaller trials that have investigated the potential benefits of TRT in elderly patients already showing evidence of age-related memory loss or cognitive impairment. Although there is some historic data from small, short-term studies that suggests that TRT in hypogonadal elderly men with no current evidence of cognitive decline may experience slight improvement in memory and cognitive function testing, more recent studies have not reported significant changes from baseline. Additionally, there is currently no evidence that serum testosterone levels accurately predict the development of Alzheimer's or other forms of age-related cognitive impairment.

Younger men with testosterone deficiency frequently report symptoms of depressed mood and irritability that quickly correct with TRT. The same effect has been observed in older men, with a recent, large randomized clinical trial reporting statistically significant, although mild, improvements in mood and alleviation of depressive symptoms for men treated with TRT compared to placebo. Importantly, the population enrolled in this study did not include a diagnosis of major depressive disorder (MDD) in the inclusion or exclusion criteria. Several studies focusing on testosterone therapy specifically in hypogonadal men with MDD have not demonstrated resolution of depressive symptoms when compared to placebo.

Although hypogonadism is a common isolated cause of erectile dysfunction among younger men, it is infrequently the sole contributing factor to impaired erectile function in older men. As such,

younger hypogonadal men receiving testosterone replacement therapy (TRT) show greater improvement in erectile function as compared to older men. However, TRT may still be an effective treatment for older men who demonstrate particularly low testosterone concentrations or when used as an adjunct to PDE-5 inhibitors. The 2018 American Urologic Association (AUA) ED Guidelines do not recommend TRT as monotherapy for the treatment of ED. However, TRT is recommended in conjunction with phosphodiesterase type 5 inhibitors (PDE5i) in hypogonadal men because PDE5i tend to be more effective in eugonadal men. Furthermore, TRT significantly increases libido in men of all ages, and as such may be an appropriate therapy for older men reporting impairment in erectile function alongside decreased sexual desire.

Low testosterone levels in older men have long been thought to increase the risk of coronary artery disease and worsen outcomes in patients with heart failure. In fact, the 2018 AUA Testosterone Guidelines state that clinicians should counsel patients with testosterone deficiency that low testosterone levels is a risk factor for cardiovascular disease. However, the guidelines go on to state that prior to initiating treatment, clinicians should counsel patients that it is not known with certainty whether TRT increases or decreases the risk of cardiovascular events. The Testosterone Replacement Therapy (TRT) on the Incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measures in Hypogonadal Men (TRAVERSE) Trial is set to be completed in June of 2022. This trial is the largest randomized placebo controlled TRT trial assessing time to major adverse cardiac event, which includes nonfatal MI, nonfatal stroke or death due to cardiovascular causes. It is anticipated that this trial will shed further light on the true relationship between TRT and cardiovascular risk.

There are many potential benefits of TRT in aging men, but the side effect profile of testosterone replacement should always be kept in mind. Common side effects of TRT include fluid retention, gynecomastia, polycythemia, and potentially exacerbation of sleep apnea. For these reasons, all men receiving TRT should be closely monitored by the prescribing physician throughout the duration of treatment.

In an older male patient with symptoms consistent with hypoandrogenism but with normal testosterone levels on laboratory testing, it is prudent to search for other causes of the patient's symptoms. Many other pathologies or drug side effects may cause many of the symptoms associated with low testosterone and these

etiologies should be further explored. The formulations of testosterone approved by the Food and Drug Administration (USA) as of 2021 can be seen in Table 1, Chapter 52).

DHEA

Levels of DHEA typically peak in the third decade of life, after which there is a gradual decline in serum concentration. By the time men are between 70-80 years of age, DHEA concentrations are approximately 20% of what they were at their peak. As a result, DHEA is frequently marketed as an over-the-counter supplement to prevent symptoms of aging. However, currently available data limits the understanding regarding both the potential benefits and harms of DHEA supplementation in older men.

Available data does suggest that DHEA causes statistically significant improvement in bone density in older men compared to placebo; however, the improvements are mild and much less than is achieved with other currently available treatments for osteoporosis. In regard to cognitive functioning and mood, small studies have produced conflicting data. Although some studies did report some slight improvement in episodic memory and mild improvements in mood, just as many studies report no significant changes within these domains. Additionally, although DHEA is converted *in vivo* to other more potent androgens, supplementation has not shown any statistically significant improvements in libido or erectile dysfunction among older men.

There are currently no studies detailing adverse outcomes of DHEA supplementation. Although several sources discuss a theoretical risk of progression of hormone sensitive cancers (e.g., prostate and breast) or increased prostate volume, there is no data supporting these hypotheses currently available in the literature. At present, there is insufficient data to recommend routine DHEA supplementation to prevent the physiologic changes related to aging in men. Although there are no known adverse effects of supplementation, any potential benefits are thought to be insignificant.

Growth Hormone

Similar to testosterone and DHEA, growth hormone and IGF-1 levels gradually decline as men age. However, it is currently illegal in the United States to prescribe growth hormone as an anti-aging treatment. Given the known influence of growth hormone in younger

populations on body composition and metabolic function, it has been theorized that supplementation in older adults may alleviate symptoms of aging. However, currently available studies have failed to demonstrate significant clinical benefit. A handful of clinical trials have shown a mild increase in lean body mass with a corresponding decrease in body fat; however, no other improvements in metabolic function or body composition have been noted.

Additionally, there are known adverse effects of growth hormone supplementation that have limited further study. Frequently observed side effects include carpel tunnel syndrome, insulin resistance, edema and arthralgias. There are to date no studies detailing cancer risk in older patients receiving growth hormone supplementation.

Suggested reading

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